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| EXAMINER | |
|---|---|
| OGUNBIYI, OLUWATOSIN A | |
| **ART UNIT** | **PAPER NUMBER** |
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| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/537,583 | VOUSDEN, KATHERINE ANN | |
| | Examiner | Art Unit | |
| | Oluwatosin Ogunbiyi | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 14-22* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6-11 and 17* is/are rejected.

7)☐ Claim(s) *2,4,7 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Priority*

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Specification*

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 1 line 42, page 2 line 28 and 29). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### *Information Disclosure Statement*

3. The information disclosure statement filed 8/30/2005 has been considered. An initialed copy is enclosed.

### *Election/Restrictions*

4. Applicant's election without traverse of claims of Group I, namely claims 1-11 and 17 in response to election/restriction requirement of 8/29/2006 is acknowledged.

Claims 14-16 and 18-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/2/2006.

### *Claim Objections*

5. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The instant claim is drawn to a function conservative variant of CCA1 (ATP(CTP):tRNA nucleotidyltransferase enzyme). The independent claim (claim 1) from which this claim

depends from utilizes fungal CCA1. The term 'function conservative variant' in the instant claims broaden by including proteins that possess CCA1 enzyme activity from non-fungal sources. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

6. Claims 4,7 and 11 are objected to because of the following informalities: the instant independent claims contain the acronyms CCA1(ATP(CTP):tRNA nucleotidyltransferase enzyme). While acronyms are permissible shorthand in the claims, the first recitation (i.e. in an independent claim) should include the full recitation followed by the acronym in parenthesis. Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 11 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn towards *Candida* or *Aspergillus* CCA1(ATP(CTP):tRNA nucleotidyltransferase enzyme). The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Applicant (s) can modify the claim to reflect the "hand of man" by reciting " an isolated or purified' provided the specification provides support for such modification.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 2 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of screening or testing for candidate anti-fungal compounds that impair CCA1 (ATP (CTP): tRNA nucleotidyltransferase enzyme) function by determining the interaction of the candidate compound with said CCA1, wherein the CCA1 comprises a fragment, a function-conservative variant or an active fragment.

CCA1 (ATP (CTP): tRNA nucleotidyltransferase) also known amongst many synonyms as tRNA nucleotidyltransferase or CCA-adding enzyme is a ubiquitous enzyme that catalyzes the incorporation of CMP and AMP into incomplete tRNA chains. The enzyme is required for normal growth of cells and is involved in repair of tRNA molecules that are missing part of the 3' terminus. The substrates for the enzyme include ATP and tRNA (See introduction of Navarro et al. 1991, Italian Journal of

Biochemistry; 40(5) pages 295-303 and review article, Weiner, 2004. Current Biology, vol. 14, issue 20 pages R883-R885).

The specification does not provide any definition or guidance as to the structural, physical or chemical characteristics of CCA1 fragments, function conservative variants or active fragments that function similarly as the CCA1 enzyme. Although, the specification defines fragment, active fragment and function-conservative variant, the specification and the claims do not provide any guidance on the structure of CCA1 comprising fragments, function conservative variants or active fragments. Furthermore, the recitation of 'CCA1" does not convey a common structure or function for the "function conservative variant", fragment or active fragment of CCA1 as claimed. There are no sufficient identifying characteristics of a function conservative variant or active fragment; they are described only by a functional characteristic without any known or disclosed correlation between the biological function and structural characteristics. *In re Bell* F.2d 781, 26 USPQ2d (Fed. Cir 1993).

The scope of the claims encompasses numerous structural species resulting in a highly variant genus composed of members with a significant number of structural differences. The disclosure fails to describe the common attributes or structural characteristics that identify members of said genus and because the genus is highly variant, the function of the CCA1 enzyme alone is insufficient to describe the genus of CCA1 proteins that function equivalently. The genus of fragments of CCA1 is large and ranges from a single amino acid to the inactive fragment of CCA1 to the active fragment of CCA1 to the whole CCA1 protein. The general knowledge and level of skill in the art does not supplement the omitted description of such function conservative variants or fragments or active fragments because specific, not general guidance is needed. The specification fails to teach the nucleotide sequences or amino acid sequences or crystal structure or active sites of any CCA1 as a reference for an artisan skilled in the art to compare in order to identify characteristics of a CCA1 fragment, a function conservative variant or a active fragment.

One of skill in the art would reasonably conclude that the disclosure of the accession numbers (specification page 2 lines 24-30) disclosing the polypeptide of

CCA1 fails to provide a representative number of species to describe the claimed genus of a CCA1 fragment, a function conservative variant or a active fragment and as such the specification lacks written description for the highly variant genus claimed and one of skill in the art would not recognize that applicants had possession of the genus of the claimed fragments or function conservative variant as instantly claimed.

9. Claims 9, 10, 11 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are reach through claims and are drawn to products identified by a method of screening or testing for candidate anti-fungal compounds that impair CCA1 (ATP (CTP): tRNA nucleotidyltransferase enzyme) function and to a compound or inhibitor identified by said method that impairs CCA1 function compound for use as an antifungal compound, a composition comprising a CCA1 inhibitor and *Candida* and *Aspergillus* CCA1 as a specific target for antifungal compounds.

The specification does not teach the structural or specific functional characteristics of any compound, that impairs CCA1 function, and also there is no known or disclosed correlation between the physical and chemical characteristics of a compound and its function in impairing CCA1. Furthermore, there is no indication in the specification that the method used to identify the compound that impairs CCA1 activity is actually implemented.

An adequate written description of a chemical invention also requires a precise definition such as by structure, formula, chemical name or physical properties and not merely a wish or plan for obtaining the chemical invention claimed. See *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). While there is description of an assay for screening compounds to identify those that impair CCA1, there is no disclosure of which compound selectively impairs CCA1. Without such a disclosure the claimed method and compound is not described.

As to claim 11, drawn to *Candida* or *Aspergillus* CCA1 as a specific target for antifungal compounds, the disclosure does not disclose any antifungal compound(s) that target and impair *Candida* or *Aspergillus* CCA1 nor is there any description of the large genus of *Candida* or *Aspergillus* CCA1. Without physical, chemical, structural characteristics of such a compound that impairs the genus of *Candida* or *Aspergillus* CCA1 and a correlation with function as an antifungal compound by impairing CCA1 one of skill in the art would not be able to determine whether the genus of *Candida* or *Aspergillus* CCA1 is a specific target for antifungal compounds.

In summary, one of skill in the art would reasonably conclude that the disclosure does not provide adequate description for the method of screening or testing for candidate anti fungal compounds that impair CCA1 in the instant claims since no physical, chemical and functional characteristics as it pertains to impairment of CCA1 for said claimed compound/inhibitor is disclosed. Thus, one of skill in the art would not recognize that applicants had possession of the compound/inhibitor that impairs CCA1 from any fungal organism including *Candida* or *Aspergillus*.

10. Claims 1-3 and 8-11 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3 are drawn to a method of screening or testing for candidate anti-fungal compounds that impair CCA1 enzyme function and a compound identified by said method comprising (a) providing fungal CCA1 (b) providing one or more candidate compounds (c) contacting said CCA1 with said one or more candidate compounds and (d) determining the interaction of the candidate compound with said CCA1.

Claim 8 is drawn to a method of screening or testing for candidate anti-fungal compounds that impair CCA1 enzyme function and a compound identified by said method comprising (a) providing fungal CCA1 in an eukaryotic cell (b) providing one or more candidate compounds (c) contacting said eukaryotic cell with said one or more

candidate compounds and (d) determining the interaction of the candidate compound with said CCA1 by assessing the effect on growth or viability of said cells.

Furthermore, claims 9-11 and 17 are drawn to a compound identified by the method of claim 1 (claim 9), a pharmaceutical composition comprising a CCA1 inhibitor and a pharmaceutically acceptable carrier (claim 10), *Candida* or *Aspergillus* CCA1 as a specific target for antifungal compounds (claim 11) and a compound identified by the method of claim 8 (claim 17).

CCA1 or (ATP (CTP):tRNA nucleotidyltransferase also known amongst many synonyms as tRNA nucleotidyltransferase or CCA-adding enzyme is an ubiquitous enzyme that catalyzes the incorporation of CMP and AMP into incomplete tRNA chains. The enzyme is required for normal growth of cells and is involved in repair of tRNA molecules that are missing part of the 3' terminus. The substrates for the enzyme include ATP or CTP (a nucleotide) and tRNA and the enzyme can utilize nucleotide analogs to catalyze its reaction. The enzyme has a nucleotide binding site and an active site. (See introduction of Navarro et al. 1991, Italian Journal of Biochemistry; 40(5) pages 295-303, review article, Weiner, 2004. Current Biology, vol. 14, issue 20 pages R883-R885, see other relevant art under citation of relevant art below).

As to claims 1-3, 8 the specification teaches that the methods of the invention provide a facile and specific assay to screen compounds that impair CCA1 function as potential antifungal compounds (page 4 line 2). The method steps disclosed comprises 'determining the interaction of the candidate compound with said CCA1'. The specification teaches that the in screening methods of the invention the candidate compound or enzyme substrate may be labeled to allow easy quantitation of the interaction between the candidate compound and the enzyme (page 4 line 16).

However, interaction of a compound with CCA1 does not predict its ability as an antifungal compound that impairs CCA1 enzyme function. Anti-fungal is defined as destroying fungi or inhibiting growth (see attached definition from Merriam-Webster Online Dictionary). The method steps and specification do not provide examples of a correlation between a compound interacting with CCA1 and the function of that compound as destroying fungi or inhibiting growth of fungi by impairing CCA1. For

example, CCA1 interacts with its substrates (CTP, ATP, tRNA) or analogs of its substrates but the interaction of the said substrates with the enzyme does not mean that said substrates impair CCA1. While a compound can interact with and impair CCA1 not all compounds that interact with CCA1 will impair the enzyme and thus will not be an antifungal. The specification does not define "impair CCA1 function" as it relates to interaction of compounds with CCA1 and antifungal activity. As an illustration, Onishi et al (Feb. 2000, Anitmicrobial Agents and Chemotherapy p. 368-377) teaches a screen for *invitro* antifungal activity of several compounds by a growth inhibition assay (page 369 column 1 materials and methods and table 1) and then the compounds were evaluated to determine whether said compounds were direct inhibitors of the enzyme by measuring the enzyme's activity in the presence of said compounds (page 370 column 2 first full paragraph, page 373 column 1 – 2 and table 4).

As to claim 8, step d, which 'recites determining the interaction of the candidate compound with said CCA1 by assessing the effect on growth or viability of said cells", The specification does not provide guidance on how said interaction is assessed by the effect on growth or viability of cells expressing fungal CCA1 and how this relates to the impairment of CCA1. Detecting inhibition of growth does not provide any knowledge about the activity of the compound on CCA1 as recited in the preamble. An anti-fungal compound has many different activities (see Ghannoum et al. 1999. Clinical Microbiology Reviews, p. 501-517 for different mode of actions of some anti-fungal compounds) and these compounds would inhibit growth but do not have to impair activity of CCA1. As such, impairment of growth is not directly correlated with impairment of CCA1 activity.

As to claims 9-11 and 17, the specification does not provide any working example of a compound identified by said screening methods that interacts with CCA1 (in claim 8, assessed by the effect on growth or viability of said cells) and impairs CCA1 activity. The specification teaches that candidate compounds that may be screened include small molecules and peptides (page 5 line 31-33). Any of these candidate

compounds may interact with CCA1 but it is unpredictable whether said compounds are antifungals that can impair CCA1 function. The specification fails to teach any compound that interacts with and impairs CCA1. Therefore, without an example and complete description of characteristics of a compound that is shown to interact with CCA1 and impair CCA1 one of skill in the art, for example, cannot design synthetic analogs of CCA1 impairing compounds or even recognize CCA1 from *Candida* or *Aspergillus* as a target for such a compound. As a general example, Onishi et al describe a compound MK-0991, a semisynthetic analog of pneumocandin B which is a known natural inhibitor of a cell wall enzyme, (1,3)-β-D-glucan synthase (see abstract).

In view of the above and especially the lack of guidance or working example of the antifungal compound that interacts with and impairs said CCA1, it would require undue experimentation of the skilled artisan to make and use the invention as claimed.

11. Claims 2-3, 9, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant dependent claims are confusing because they recite the indefinite article "A" meaning any method or product, but then attempt to limit the method or product to a particular method as presented in their respective independent claims. Amendment of the claims to change "A" to "The" would obviate this issue.

***Claim Rejections - 35 USC § 102 and 103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Prior to the below rejections, it is noted that claims 9 and 17 are product by process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP chapter 2113, Product-by-Process claims. In addition, the terms 'for use as an antifungal compound' (claims 9 and 17) and 'as a specific target for antjfungal compounds' (claim 11) are an intended use and have not been given patentable weight. Therefore, claims 9 and 17 have been interpreted for prior art purposes as drawn to a compound that impairs CCA1 function and claim 10 is drawn to *Candida* or *Aspergillus* CCA1.

12. Claims 1-2, 9 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sternbach et al. 1976. Eur. J. Biochem, 67, pg 215-221.

The claims are drawn to a method of screening or testing for candidate anti-fungal compounds that impair ATP (CTP): tRNA nucleotidyltransferase enzyme (CCA1) comprising (1) providing fungal CCA1 (2) providing one or more candidate compounds (3) contacting said CCA1 with said one or more candidate compounds; and (4) determining the interaction of the candidate compound with said CCA1 and a compound identified by such method.

Sternbach et al teaches a method of testing for inactivation of tRNA nucleotidyltransferase (ATP(CTP):tRNA nucleotidyltransferase or CCA1) by providing tRNA nucleotidyltransferase from baker's yeast (a fungus) and providing the compounds $tRNA^{Phe}$ –C-C(2'NHCOCH2Br), $tRNA^{Phe}$ –C-C(2'NHCOCH2Hg+OH) and p-hydroxymercuribenzoate and contacts CCA1 and said compounds by incubating enzyme with said compounds (Fig. 2-4). The interaction between tRNA nucleotidyltransferase and the reactive $tRNA^{Phe}$ –C-C(2'NHCOCH2Br) is determined by passing the reaction product of the reactive tRNA and the enzyme through a Sephadex G-100 column and by gel filtration (see Sephadex G-100 filtration of tRNA nucleotidyltransferase inhibitor complexes in Fig. 5).

13. Claims 1-2, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Bradley et al. WO 02/02784A1. 10 January 2002.

The claims 1-2 are set forth supra. Claim 8 is drawn to a method of screening or testing for candidate anti-fungal compounds that impair CCA1 enzyme function and a compound identified by said method comprising (a) providing fungal CCA1 in an eukaryotic cell (b) providing one or more candidate compounds (c) contacting said eukaryotic cell with said one or more candidate compounds and (d) determining the interaction of the candidate compound with said CCA1 by assessing the effect on growth or viability of said cells.

Bradley et al teaches as follows: a method of screening candidate antifungal compounds comprises providing a yeast (fungus) strain comprising an essential target

gene contacted with a candidate antifungal compound and cultured in growth media and determining the effect of said compound on growth or viability of said yeast cells (see page 69 claim 11 and page 5 lines 1-22).

Bradley et al further teach that " a candidate inhibitor...is any compound with a potential to inhibit the growth and viability of *S.cerevisiae*, or other fungi (page 31 last bridging paragraph" Bradley et al teach phenotypes associated with decreased cell viability and/or growth and example of such essential target genes including tRNA nucleotidyltransferase (page 33 line 15-24 to page 34 lines 1-4, page 36 line 8-13).

14. Claims 1, 2 and 9 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kroger et al. 1979. Eur. J. Biochem, 95, pg 341-348.

Kroger et al teaches a method of testing for inactivation of tRNA nucleotidyltransferase (ATP(CTP):tRNA nucleotidyltransferase or CCA1) by providing tRNA nucleotidyltransferase (also known as CCA1 or ATP(CTP):tRNA nucleotidyltransferase) from baker's yeast (a fungus) and providing the compounds $tRNA^{Phe}$ $-A_{73}$-$C_{74}$-$C_{75}$-$(CH_2CONH_2)s^2C_{76}$ or $tRNA^{Phe}$ $-A_{73}$-$C_{74}$-$(CH_2CONH_2)s^2C_{75}$ and contacts said CCA1 and said compounds by incubating enzyme with said compounds (page 345 column 2 and page 346 fig.3). Kroger et al also teaches that the enzyme complexes with the inhibitor ($tRNA^{Phe}$ $-A_{73}$-$C_{74}$-$(CH_2CONH_2)s^2C_{75}$ (page 346 column 1 second full paragraph and fig. 4.)

15. Claims 1, 2, 9 and 10 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Navarro et al. 1991, Italian Journal of Biochemistry; 40(5) pages 295-303.

The claims are set forth above. Claim 10 is drawn to a pharmaceutical composition comprising a CCA1 inhibitor and a pharmaceutically acceptable carrier.

Navarro et al teach a method for screening for inhibitors of tRNA nucleotidyltransferase by providing yeast tRNA nucleotidyltransferase and providing yeast extracts and contacting said tRNA nucleotidyltransferase and yeast extracts in a reaction mixture for an enzymatic assay (page 297 lines 1 and 2, and fig. 1, page 298 second full paragraph and fig 2). Navarro et al teach that a compound identified by the

above screen showed competitive inhibition with respect to ATP a substrate for the enzyme present in the reaction mixture (page 298 second full paragraph and fig. 2). Although not explicitly stated, the competitive nature of the compound shows that the compound interacts with the enzyme.

As to claim 10, Navarro et al teaches that the concentrated preparation of soluble yeast extracts, which contains the tRNA nucleotidyltransferase inhibitor, was equilibrated with water and chromatographed on a column (page 298 first full paragraph). Fractions were eluted of the column with water and collected in 0.5mL aliquots. Hence, Navarro et al teach a composition comprising a tRNA nucleotidyltransferase (CCA1) inhibitor in water. Water is known as a common pharmaceutically acceptable carrier.

16. Claim 4 and 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Deng et al. 2000, Yeast; vol 16 pages 945-952.

The claims are drawn to a modified eukaryotic cell (s) wherein the cell (s) expresses fungal CCA1 under the control of a heterologous promoter (claim 4) and wherein the CCA1 comprises a fragment, a function conservative variant , an active fragment or a fusion protein of CCA1.

Deng et al teaches modified eukaryotic *S.cerevisiae* cca 1-1 mutant cells transformed with plasmids carrying fungal (*K. lactis*) CCA1 (tRNA nucleotidyltransferase). Said transformed cells express *K. lactis* CCA1 because the *S.cerevisiae cca1-1* mutation is complemented with said plasmids comprising *Kluyveromyces lactis* (CCA 1) (fig. 4 page 9510). The plasmid pKXS containing the entire reading frame of *K. lactis* CCA1 (fig.4 lane B) or plasmid pK2 containing *K. lactis* CCA1 lacking ATGI complements the *S.cerevisae cca1-1* mutation. The transformed mutant cells express heterologous *K. lactis* CCA1 protein under a heterologous promoter present on the plasmids, which are derived from plasmid p426 (see materials and methods page 946 for construction of plasmid).

17. Claims 4, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfe et al. 1996, Journal of Biological Chemistry, vol. 271, pages 4679-4686.

The claims 4 and 7 are set forth supra. Claim 6 is drawn to a modified eukaryotic cell wherein the cell expresses fungal CCA1 under control of a heterologous promoter wherein the CCA1 is homologous.

Wolfe et al teach the heterologous expression of *S.cervisiae* CCA1 protein in a modified *S.cerevisiae (eukaryotic)* cells transformed with plasmids (pRS426, pJDB207) containing the *S.cerevisiae* CCA1 gene (homologous to *S.cerevisiae*) under the control of heterologous promoters present on said plasmids (fig.1 and column 1 second paragraph page 4681 and fig.4).

18. Claims 4, 6, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanic-Joyce et al. 2002 (published online October 31st 2002), Yeast, volume 19 pages 1399-1411.

The claims 4, 6, 7 are set forth supra. Claim 11 is drawn to *Candida* or *Aspergillus* CCA1.

Hanic-Joyce et al teach modified eukaryotic *Candida glabrata* cells (GCPI-2 is a strain in which sequences of the CCA1 (tRNA nucleotidyltransferase) gene encoding amino acids 1-476 is deleted; page 1402 column 2 paragraph 2) transformed with plasmid pRS313 derivatives encoding wild type or altered *Candida glabrata* CCA1 (homologous) (page 1204 column 1 paragraph 2 and fig.2 and 5). Said cells expresses the wildtype CCA1 or mutant CCA1 (derived from a conservative mutation) (page 1404 column 1 and fig.2).

Hanic-Joyce et al also teach Fig.3 which depicts modified *S.cerevisiae* cca1-1 mutant cells (NT33-5) transformed with plasmid pWG17-98 bearing the CCA1 gene from *Candida glabrata(* heterologous*)*. Said cells express Candida CCA1 because of he ability of the transformed cells to grow on a non-fermentable carbon source indicating that expresses Candida CCA1 was targeted to the mitochondria (page 1404 last sentence of column 2).

As to claim 11 drawn to the product *Candida* or *Aspergillus* CCA1, Hanic-Joyce et al teach the *Candida glabrata* CCA1 enzyme. Figure 1 of Hanic-Joyce et al teaches the predicted amino acid sequence of said enzyme.

19. Claims 4, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. Journal of Biological Chemistry, 1992, vol 267, pages 14879-14883.

The claims are set forth supra.

Chen et al teach a modified yeast (eukaryote) *cca1-1* mutant cells transformed with a plasmid (YCp50) carrying wildtype and mutant yeast CCA1 (homologous) genes (Fig.4.) and expressing said transformed CCA1. The yeast cells carrying said plasmids containing the CCA1 gene were able to grow demonstrating that sufficient active CCA1 protein was expressed by the cells to support life (column 2 second first full paragraph page 14881 and fig. 4b).

20. Claims 4, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Aebi et al. Journal of Biological Chemistry,1990, vol. 265, pages 16216-16220.

The claims are as set forth supra.

Aebi et al teaches heterologous overexpression of 352 protein in modified yeast cells transformed with a plasmid (pJDB207) carrying the yeast 352 gene (homologous) (page 16216 materials and methods, page 16219 column 1 first paragraph). The 352 gene shares significant homology with the *E.coli* nucleotidyltransferase enzyme (page 16220 line 4) and yeast transformants containing the 352 gene had elevated nucleotidyltransferase activity compared to cells transformed with plasmid alone (page16219 column1 paragraph 1).

21. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hanic-Joyce et al. 2002 (published online October 31st 2002), Yeast, volume 19 pages 1399-1411 and further in view of Backen et al Yeast 2000 vol. 16:1121-1129.

The claims are set forth supra.

Hanic Joyce is set forth supra. Hanic-Joyce does not teach a modified *Candida albicans* cell wherein the cell expresses fungal CCA1 under the control of a heterologous promoter.

Backen et al teaches the use of *C. albicans* cells for gene expression by transformation of said *C. albicans* cells with a vector in which a gene of interest can be placed under a heterologous CaMAL2 promoter (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to express the fungal CCA1 of Hanic-Joyce et al in *C. albicans* as taught by Backen et al resulting in the instant invention. One would be motivated to express in *C. albicans* the fungal CCA1 under the heterologous promoter of Backen et al because it provides a useful means for functional analysis of genes in *C. albicans* (abstract ) and would result in a reasonable expectation of success in view of Backen et al teaching that genes can be expressed in *C. albicans* under a heterologous promoter.

22. Claims 2 and 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al. 1996, Journal of Biological Chemistry, vol. 271, pages 4679-4686 and further in view of Invitrogen Catalog. 2000 page vii and page 79

Claims 2 and 7 is set forth supra.

Wolfe et al is set forth supra. Wolfe et al does not teach a modified eukaryotic cell wherein the cell expresses a fusion protein of CCA1 under the control of a heterologous promoter.

Invtirogen product catalog teaches several N- or C- terminal fusion tag containing vectors for high level expression of genes in the yeast *S.cerevisiae.*

It would have been prima facie obvious to one of ordinary skill in the art to transform the *S.cerevisiae* (eukaryotic) cells of Wolfe et al with any of the N- or C-terminal tagged plasmids of Invitrogen further comprising *S.cerevisiae* CCA1 under the control of a heterologous promoter of said plasmids in order to obtain an eukaryotic cell which expresses a fusion protein of CCA1 with a reasonable expectation of success. Invitrogen product catalog provides a motivation to do so which is that the tags on the fusion protein allow for convenient detection and purification.

*Citation of Relevant Art*

- Yue et al (1998). The CCA-adding enzyme has a single active site. J. Biol. Chem. 273:29693-29700
- Cho et al (2003). Use of nucleotide analogs by class I and class II CCA-adding enzymes (tRNA nucleotidyltransferase): deciphering the basis for nucleotide selection. RNA 9, 970-981.

***Status of the Claims***

No claim is allowed.

***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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